

(19)



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(11)

EP 0 940 385 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
25.06.2003 Bulletin 2003/26

(51) Int Cl.7: **C07C 213/10**

(21) Application number: **99104275.5**

(22) Date of filing: **03.03.1999**

(54) **Process for the separation of the
(RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)-cyclohexanol isomer from the (RS,SR)
isomer by selective precipitation**

Verfahren zur Abtrennung des
(RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)-cyclohexanolisomers von dem (RS,SR)
Isomer durch selektive Ausfällung

Procédé de séparation de l'isomère (RR,SS) du
(dimethylamino)methyl-2-(3-methoxyphenyl)-1-cyclohexanol de l'isomère (RS,SR) par précipitation
sélective

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

(30) Priority: **06.03.1998 IT MI980457**

(43) Date of publication of application:
08.09.1999 Bulletin 1999/36

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**EP-A- 0 778 262 EP-A- 0 831 082
US-A- 3 652 589 US-A- 5 414 129**

Remarks:

The file contains technical information submitted
after the application was filed and not included in this
specification

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Description

[0001] The present invention relates to a method for the purification of (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol (also named trans-(±)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)-cyclohexanol) based on a selective crystallization procedure.

[0002] (RR,SS)-2-(Dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol in the form of hydrochloride is an active ingredient belonging to the class of analgesics, which has been used in therapy since 1978, under the non-proprietary name Tramadol (Schenk, E.G.; Arend, I. *Drugs* **1978**, 28, 209). More particularly, this compound is used against acute and chronic pains, as it acts on opioid receptors and inhibits serotonin and noradrenalin reuptake. Compared with other medicaments of the same class, it interestingly causes comparatively low tolerance (Preston, K.L.; Jasinski, D.R.; Testa, M. *Drug and Alcohol Dependence* **1991**, 27, 7) and poor side effects (Cossmann, M.; Kohen, C. *Rev. Contemp. Pharmacother.* **1995**, 513). However, the product should be highly pure for these therapeutic effects to take place. The synthetic method comprises reacting 3-bromo-anisole via Grignard reagent with 2-dimethylaminophenylcyclohexanone to give the two diastereomers (RS,SR)- and (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)-cyclohexanol in ratios ranging from 30/70 to 85/15. The purification of the trans form from the cis form is critical for the preparation of Tramadol for the pharmacological use. The known methods are substantially two:

1. A process which makes use of dioxane to recrystallize the hydrochloride of the diastereomeric mixture (Von Frankus, E.; Friderichs, E.; Kim, S.M.; Osterloh, G. *Arneim.Forsch.Drug Res.* 1978, 28, 114; Flick et al. US 3652589). Dioxane is however a toxic solvent, which involves safety problems when used in industrial plants as well as very low tolerance limits on the end product (<5 ppm).

2. The selective precipitation of the trans isomer by preparing the hydrochloride of the Grignard reaction crude by means of gaseous HCl in solvents such as alcohols, ketones, esters etc. (US 5414129, Chemagis). On the other hand, as it is evidenced in the experimental section, this method yields a product which cannot be marketed and used in therapy. The resulting hydrochloride has to be repeatedly recrystallized.

[0003] EP-A-0778262 discloses a process for the purification of (RR, SS)-2-dimethyl-aminomethyl-1-(3-methoxyphenyl) cyclohexanol and its salts from mixtures also containing the (RS, SR) isomer comprising reacting the above mixture in a solvent at elevated temperature under acidic conditions, selectively precipitating the desired (RR, SS) isomer as an amine acid

salt, and recrystallizing the purified product.

[0004] EP-A-08 31082 published on 25.03.98, discloses a process for the purification of (RR, SS)-2-dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol hydrochloride from a mixture containing the cis and trans isomers, which process includes combining the mixture with an electrophilic reagent, the reagent selectively reacting with the hydroxyl group of (RS, SR)-Tramadol, leaving most of the (RR, SS) Tramadol intact, and precipitating the remaining, practically pure (RR, SS) Tramadol from the mixture.

[0005] It now has been found that (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol **III** can be recovered as crystalline solid from a solvent consisting of water and a water-miscible organic solvent such as acetone, DMF, ethanol, methanol, THF. The recovery of (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)-cyclohexanol of formula **III** as a solid is surprising in that the very same product had been described to be a liquid (Flick et al.; US 3652589), and it is advantageous since it makes the purification from the other isomer easier, as the latter is oily. Therefore, the solid isomer can be removed selectively from (RS,SR)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)-cyclohexanol of formula **IV**.

[0006] The selective precipitation according to the invention takes place using mixtures of water and water-miscible organic, solvent in ratios ranging from 9:1 to 1:9 respectively, preferably of about 1:1.

[0007] Preferred organic solvents are C₁-C₃ alcohols (methanol, ethanol, isopropanol), acetone, methyl ethyl ketone, dimethylformamide, tetrahydrofuran, diglyme, glycols, preferably methanol, ethanol, acetone and tetrahydrofuran.

[0008] The crystallization temperature is not critical, but it will generally range from 10°C to -40°C.

[0009] The crude is obtained by preparation of 3-bromo-anisole Grignard reagent **II** and subsequent condensation with 2-dimethylaminomethyl cyclohexanone **I** according to the procedure disclosed in US 3652589.

[0010] The process of the invention is illustrated in the following examples.

EXAMPLE 1

[0011] The oily mixture containing the two tramadol isomers as bases (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol **III** and (RS,SR)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol **IV** (104 g) is added with H₂O (300 ml) and formic acid to complete dissolution, followed by acetone (300 ml) and NaOH to basic pH. The solution is cooled to 0-5°C. The precipitate is filtered and washed with H₂O. The humid product is transformed into the corresponding hydrochloride in toluene at 60°C using gaseous HCl to yield 100 g with a HPLC diastereomeric purity >99.8%.

EXAMPLE 2

[0012] The same procedure as in Example 1 was followed, using ethanol instead of acetone, to obtain 95 g of the product.

EXAMPLE 3

[0013] The same procedure as in Example 1 was followed, using THF instead of acetone, to obtain 98 g of the product.

EXAMPLE 4

[0014] The same procedure as in Example 1 was followed, using methanol instead of acetone, to obtain 97 g of the product.

Claims

1. A process for the purification of (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol, which comprises the selective precipitation of (RR,SS)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol in the presence of (RS,SR)-2-(dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol from a solvent consisting of water and a water-miscible organic solvent.
2. A process as claimed in claim 1, in which the water-miscible organic solvent is selected from C₁-C₃ alcohols, acetone, methyl ethyl ketone, dimethylformamide, tetrahydrofuran, glycols, diglyme.
3. (RR,SS)-2-(Dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol in the solid form.

Patentansprüche

1. Verfahren zur Reinigung von (RR,SS)-2-(Dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol, das umfaßt: Selektives Ausfällen von (RR,SS)-2-(Dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol in Gegenwart von (RS,SR)-2-(Dimethylamino)methyl-1-(3-methoxyphenyl)cyclohexanol aus einem Lösungsmittel, das aus Wasser und einem wassermischbaren, organischen Lösungsmittel besteht.
2. Verfahren nach Anspruch 1, worin das wassermischbare, organische Lösungsmittel ausgewählt wird aus: C₁-C₃-Alkoholen, Aceton, Methylethylketon, Dimethylformamid, Tetrahydrofuran, Glykolen, Diglyme.
3. (RR,SS)-2-(Dimethylamino)methyl-1-(3-methoxy-

phenyl)cyclohexanol in fester Form.

Revendications

1. Procédé pour la purification de (RR,SS)-2-(diméthylamino)méthyl-1-(3-méthoxyphényl)cyclohexanol, qui comprend la précipitation sélective de (RR,SS)-2-(diméthylamino)méthyl-1-(3-méthoxyphényl)cyclohexanol en présence de (RS,SR)-2-(diméthylamino)méthyl-1-(3-méthoxyphényl)cyclohexanol à partir d'un solvant constitué par de l'eau et un solvant organique miscible avec l'eau.
2. Procédé selon la revendication 1, dans lequel le solvant organique miscible avec l'eau est choisi parmi les alcools en C₁ à C₃, l'acétone, la méthyléthylcétone, le diméthylformamide, le tétrahydrofurane, les glycols, le diglyme.
3. (RR,SS)-2-(Diméthylamino)méthyl-1-(3-méthoxyphényl)cyclohexanol sous forme solide.